REMARKS

STATUS OF THE CLAIMS.

Claims 2-6, 9-16, 18-20, 23, 25, 26, and 43-45 are pending with entry of this amendment, claim 17 being canceled. Claims 13, 14, and 16 are amended herein. In particular, formerly independent claims 13 and 14 have been rewritten as dependent claims, and an element previously recited in claim 17 has been incorporated into claim 16. Thus, these amendments introduce no new matter.

DRAWINGS.

The Examiner has indicated that Figure 11, filed on June 4, 2004, was not present in the original specification and therefore constitutes new matter. Office Action, page 2. Applicants respectfully point out that Figure 11 was present in Appendix A to the originally specification. A copy of page 3 of Appendix A, as filed, which shows Figure 11, is attached for the Examiner's convenience. Also attached is a copy of the date-stamped Receipt Acknowledgement Postcard, which evidences that the Patent Office received Appendix A, with the rest of the specification, and accorded a filing date of December 6, 2001. Withdrawal of the new matter rejection of Figure 11 is therefore respectfully requested.

35 U.S.C. §112, FIRST PARAGRAPH.

Claims 2-6, 9-20, 23, 25, 26, and 43-45 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Office Action, page 2. The rejection is respectfully traversed.

In particular, the Examiner contends that the specification fails to enable an artificial tissue comprising a microvessel, wherein the microvessel produces a blood cell. *Id.*, pages 2-3. Claim 16, which previously recited that "the one or more microvessels produce one or more blood cells," has been amended to substitute the term "mononuclear leukocytes" for "blood cells." As noted previously, the application contains a working example in which an artificial tissue according to the invention produced microvessels, which produced mononuclear leukocytes. Specifically, Appendix A stated:

> When the endothelial cells develop into larger vessels we observe the presence of leukocytes inside these vessels (A). (B-E) High magnification of regions in (A) to illustrate the presence of these leukocytes. (F) Blood cell immunolabeled with an antibody for macrophage scavenger receptor (mSR), a specific protein for these leukocytes. (G) Blood cells stained with an antibody to CD68 also a cell surface marker for mononuclear leukocytes. Summary: Under our culture conditions, endothelial cells are able to differentiate into mononuclear leukocytes.

This text has been incorporated into the specification at page 4, after line 19 (as the description for Figure 16).

Applicants appreciate the Examiner's acknowledgement in the Office Action that "the claimed invention is enabled to the scope of the artificial skin with microvessels that produces [*sic*] mononuclear leukocytes." Office Action, page 3. The pending claims either do not require the production of any blood cell (all pending claims except claim 16) or require the production of one or more mononuclear leukocytes (claim 16). Accordingly, Applicants respectfully submit that the specification fully enables the pending claims. Withdrawal of the § 112, first paragraph rejection is therefore respectfully requested.

35 U.S.C. §103.

Black and Li

Claims 13 and 14 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Black *et al.* (1998, FASEB J. 12, 1331-1340), in view of Li *et al.* (2000, PNAS 275, 35384-35392). Office Action, page 4. The rejection is respectfully traversed.

Claims 13 and 14 were formerly independent claims relating to an artificial tissue comprising various cell types and Vitrogen™, a type I collagen. Black is cited as teaching the combinations of cells, and Li is cited as teaching the use of Vitrogen™. *See id.* Claims 13 and 14 now depend from independent claim 23. Claim 23 recites:

> An artificial tissue produced by a method comprising: mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture and forming ***a culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells***, wherein said endothelial cells contact inner surfaces of the support matrix-connective tissue mixture layers, and wherein the cells are from the same species.

(Emphasis added.) Black cultured connective tissue cells and/or endothelial cells on ***top*** of a support matrix that consisted of a chitosan/collagen biopolymer, and plated keratinocytes on top of these cultures. *See* Black, page 1333, col. 1. Li studied smooth muscle cell migration on membranes coated with the type I collagen Vitrogen®. Li, page 35385.

Neither Black, nor Li, teaches or suggests the recited sandwich-type configuration for the culture used to make the tissue. As the combination of Black and Li fails to teach or suggest all of the elements of claims 13 and 14, withdrawal of the § 103 rejection over Black, in view of Li, is respectfully requested.

Black and Montesano

Claims 2-6, 11, 12, 15, 18-20, 23, 25, 26, 43, and 45 are rejected under § 103(a) as unpatentable over Black, in view of Montesano (1983, J. Cell Biol., 97, 1648-52). Office Action, page 5. The rejection is respectfully traversed.

Of the rejected claims, only claim 23 is independent. The Examiner acknowledges that "Black et al. do not each an artificial tissue comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells." *Id.* The Examiner believes that Montesano remedies this deficiency. Montesano teaches growing capillary endothelial cell monolayers on the surface of a collagen gel and then covering the monolayer with a second layer of collagen. Montesano, abstract. Montesano also teaches mixing endothelial cells in gelling collagen solutions. Montesano, page 1649, col. 2.

However, claim 23 requires mixing of connective tissue cells (e.g., dermal fibroblasts) with a support matrix and layering the mixture on either side of an endothelial cell layer. Montesano does not teach or suggest the use of connective tissue cells. Black teaches the use of fibroblasts, but only on top of a support matrix. Accordingly, the combination of Black and Montesano fails to teach or suggest "mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture and forming a culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells," as recited in claim 23. As this combination fails to teach or suggest all of the elements of claim 23, this claim is clearly patentable over Black and Montesano. The other rejected claims are patentable over the cited combination at least by virtue of their dependence from claim 23. Withdrawal of the § 103 rejection over Black, in view of Montesano, is therefore respectfully requested.

Black, Montesano, and Li

Claim 9 stands rejected under § 103(a) as unpatentable over Black, in view of Montesano and Li. Office Action, page 6. The rejection is respectfully traversed.

Claim 9 recites: "The artificial tissue of claims 2 or 23 wherein the support matrix comprises Vitrogen®." Claim 2 depends from claim 23, and thus claim 9 incorporates all of the elements of claim 23. The Examiner believes that Black and Montesano suggest the artificial tissue of claim 23, but notes that these references "do not teach making an artificial tissue using Vitrogen®." *Id.*

However, as explained above, the Black-Montesano combination fails to teach or suggest "mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture and forming a culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells," as recited in claim 23. Li fails to teach or suggest any sandwich-type configuration, much less one in which the outer layers include connective tissue cells. Thus, Li fails to remedy the deficiency of the Black-Montesano combination. Accordingly, Black, Montesano, and Li fail to teach or suggest all of the elements of claim 9. Withdrawal of the § 103 rejection over this combination of references is therefore respectfully requested.

Black, Montesano, and Lokeshwar

Claim 2, 10, 23 and 44 were rejected under § 103(a) over Black, in view of Montesano and Lokeshwar *et al.* (2000 J. Biol. Chem. 275:27641-49). Office Action, page 7. The rejection is respectfully traversed.

Of the rejected claims, only claim 23 is independent. Specifically, claim 2 depends from claim 23, and claim 44 depends from claims 2 or 23; claim 10 depends from claim 44. Claim 10 recites that the claimed artificial tissue includes primary human adult lung microvascular cells.

In explaining the rejection, the Examiner stated:

> The teachings of Black et al. [and] Montesano et al. are discussed above. However Black et al. and Montesano et al. do not teach making an artificial tissue using endothelial cells [that] comprise primary human lung microvascular cells.

> Lokeshwar et al. teach that primary human endothelial cell culture is established by culturing human lung microvessel cells (hMEVC-L) purchased from Clonetics/Biowhittaker Inc. (see page 27642, 1st col., 4th paragraph, lines 1-3.

Office Action, page 7. Thus, Lokeshwar was apparently cited as teaching the element recited in claim 10.

The combination of Black and Montesano fails to teach or suggest "mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture and forming a culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells," as recited in claim 23. Lokeshwar does not teach or suggest an artificial tissue including a support matrix, together with the multiple cell types recited in the pending claims. Therefore, Lokeshwar fails remedy this deficiency of the Black/Montesano combination. For at least this reason, these cited references fail to teach or suggest the artificial tissue of claim 23 or of claims 2, 10, or 44, which depend, directly or indirectly, from claim 23. Withdrawal of the § 103 rejection over Black, Montesano, and Lokeshwar is therefore respectfully requested.

CONCLUSION.

In view of the foregoing, Applicant believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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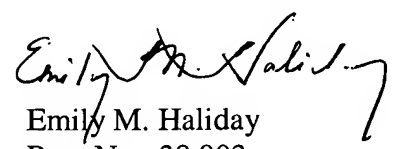
Respectfully submitted,



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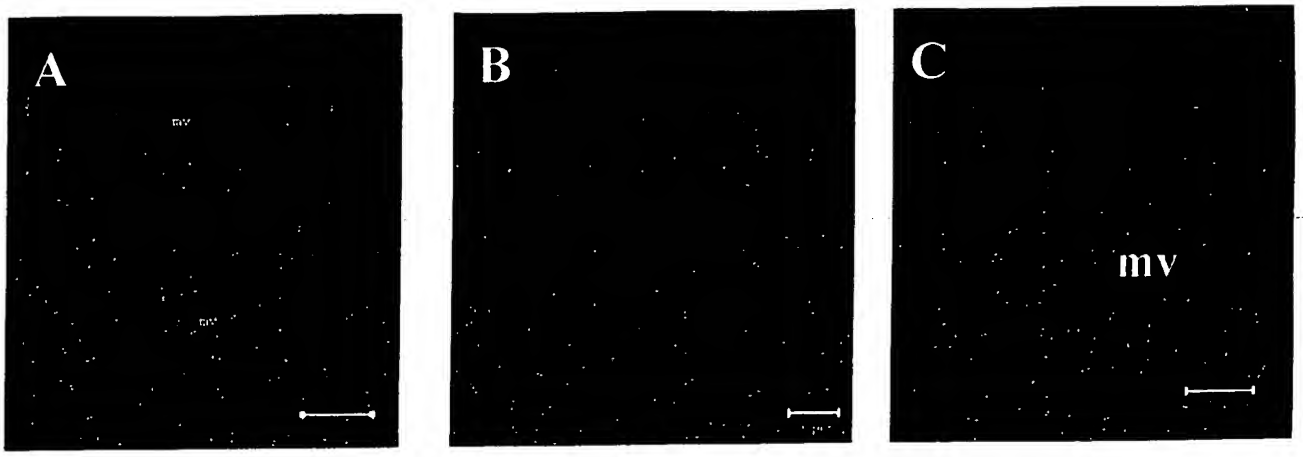
To characterize this organ culture system we used a variety of antibodies to human cell surface proteins and ECM molecules to determine whether this system develops the characteristics of human skin.



WGA ConA Red: PECAM-1 Green: HA Blue: Nuclei

To detect the presence of glycosylated molecules on the cell surface and on ECM molecules, we used fluorochrome-conjugated lectins that bind specific sugars. Wheat Germ Agglutinin (WGA) specifically binds to N-acetylglucosamine and N-acetylneuraminic acid and Concanavalin A (Con A) selectively recognizes α-mannopyranosyl and α-glucopyranosayl. Both lectins stain all of the components of the organ culture. We also stained for hyaluronic acid (HA, a glucosaminoglycan that is present in areas of blood vessel remodeling) using biotinylated hyaluronic acid binding protein which binds to HA at specific site along the in the molecule. We observed punctated staining in the extracellular matrix regions, in particular in the areas surrounding the microvessels.

PATENT APPLICATION
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Attorney:STH:afa
Title:ENGINEERED ANIMAL TISSUE

__X__ Declaration (unsigned)
_____ Assignment
_____ Combined Declaration & Power of Attorney
__X__ 18 pages of Appendix A & I
_____ Small Entity Declaration

No. of Claims:	42	
No. of Pages of Description:	40	(Specification, Claims, Abstract)
No. of Pages of Abstract:	01	
No. of Pages of Drawings:	06	
Cover page	01	
Data Entry sheet(s)	02	
Transmittal Letter/Fee Sheet	01	

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